UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/419,517	10/18/1999	WAYNE H. KAESEMEYER	97-092-US-C2	1371

7590 06/13/2003

Raymond A Miller c/o Pepper Hamilton LLP
500 Grant Street 50th floor
Pittsburgh, PA 15219-2502

EXAMINER
KIM, JENNIFER M

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/419,517	KAESEMEYER, WAYNE H.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,12,13 and 16-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,12,13,16-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 12, 13, 16-19 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,968,983. Although the conflicting claims are not identical, they are not patentably distinct from each other because it encompasses same subject matter. The diseases or disease conditions to be treated and the active agents to be employed in the instant Application are claimed and taught by the patent. Therefore, it would have been obvious to one of ordinary skill in the art to employ the active agents for the treatment of the diseases conditions well taught by the patent.

Moreover, the mechanism of action set forth in the claim 16 that stimulating Nitric Oxide Synthase by administering L-arginine and an HmgCoA reductase inhibitor is obviously

achieve by the method of treating a disease condition set forth in claim 3 of the patent. That applicant may have determined a mechanism by which the active ingredient gives the pharmacological effect does not alter the fact that the compound has been previously used to obtain the same pharmacological effects which would result from the claimed method. The patient, condition to be treated and the effect are the same. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims.

Response to Arguments

Applicants' arguments filed April 7, 2003 have been fully considered but they are not persuasive. Applicants argue that the specific list of the inhibitors of HmG-CoA reductase inhibitors were "by way of example only" and atorvastatin and cerivastatin were both implicitly and inherently disclosed in the application as originally filed. This is not persuasive because atorvastatin and cerivastatin are not explicitly disclosed or taught by the original application as filed and there is no literal support of these two agents. Therefore at the time that instant Application was filed, Applicants had no possession of the claimed specific active agents (i.e. atorvastatin and cerivastatin) and an Affidavit under Rule 131 using the prior patent would not serve as a clear evidence of prior conception and reduction to practice. Applicants argue that Applicant's original disclosure predates the filing date of U.S.Patent No. 6,147,109 to Liao since the disclosure of page 9, lines 13-14 of the Application that "L-arginine being used in "conjunction with virtually any of the family of those substances known as Hmg-CoA

reductase inhibitors". This is not persuasive because as commented above, atorvastatin and cerivastatin are not explicitly disclosed or taught by the original application as filed and there is no literal support of these two agents any where in the Application. Therefore, the Liao patent is applicable and anticipates Applicants' claims. Applicants argue that Morris's teaching of an obscure Hmg-CoA reductase inhibitor arginine salt, without any suggestion, motivation or otherwise rationale for using it to treat a disease state in no way anticipates or make obvious the present invention. This is not persuasive because Morris et al. clearly teach a novel Hmg-CoA reductase inhibitor with a suggestion of its optimum salt form (i.e. arginine salt). It is well known that Hmg-CoA reductase inhibitors are known to treat hypercholesterolemia and it is also well admitted by the Applicants (page 1, lines 8-18, DESCRIPTION OF RELATED ART). It is noted that claims 1,2,5,6,12,13 16 and 17 are drawn to any disease conditions therefore, it would have been obvious to one of ordinary skill in the art to employ a novel Hmg-CoA reductase formulated with its optimal salt form as taught by Morris et al in treatment of any disease conditions (i.e. hypercholesterolemia) as well known to be treated with a Hmg-CoA reductase. Applicants argue that the Examiner has shown no suggestion of motivation to combine the elements and no reasonable expectation of success of rejection of claims 1-6, 12,13,16-19 and 22 over U.S.Patent No. 5,634,895 to McGovern et al. and U.S.Patent No. 5,634,895 to Igo et al. This is not persuasive because each of the active agents are taught by the prior art to treat the diseases that are related to coronary heart and cardiovascular conditions (i.e. restenosis and angioplasty). Therefore it would be expected that the combination of

components would treat the diseases related to coronary heart or cardiovascular diseases as well. Applicants argue that cerivastatin, atorvastatin and L-arginine are described in the art are not used for the same purpose therefore, these teachings do not satisfy a prima facie case of obviousness. This is not persuasive because all of the active agents are involved in inhibiting or preventing atherogenesis condition as taught by the cited references. Therefore, the combination of the each of the components would prevent or inhibit atherogenesis as well. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

In view of the above Office Action of 11/5/2002 is deemed proper and asserted with full force and effect herein to obviate applicants' claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 21 and 23-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The active agents,

atorvastatin and cerivastatin in claims 20, 21 and 23-26 lack literal support in the specification as filed. This is a New Matter rejection.

It is suggested to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. Claims 20,21 and 23-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Liao et al.(U.S.Patent No. 6,147,109) of record.

Liao et al. at the abstract, column 9, lines 10- 27(particularly lines 26 and 27), column 10, lines 19-27(particularly line 27), teach applicants method and the therapeutic mixture comprising treating a disease condition in a subject comprising administering a mixture of L-arginine and Hmg-CoA reductase (atorvastatin or cerivastatin).

Since the Applicants' disclosure of atorvastatin and cerivastatin is not taught in the parent Application serial No. 08/833842, the benefit of priority date of the parent Application does not apply in instant rejection.

Therefore Applicant's priority date of above claims is the filing date of instant Application of October 18, 1999.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,2, 5, 6, 12, 13, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morris et al.(1994).

Morris et al. teach on the abstract that the optimal salt form for a novel HMG-CoA reductase inhibitor, BMS-180431 in oral dosage form is the arginine salt.

Morris et al. also on the abstract teach that above salt selection process can be easily adopted in the drug development program and can be completed within 4 to 6 weeks.

The difference between above reference and Applicant's claimed invention is lack of illustrated example of the novel HMG-CoA reductase with arginine salt for treating a disease condition. However, the skilled artisan would be motivated to employ HMG-CoA reductase together with arginine salt for treatment of hypercholesterolemia since

the HMG-CoA reductase with arginine salt form is the optimal salt form for the novel HMG-CoA reductase inhibitor, BMS-180431. The skilled artisan would be motivated with reasonable expectation of success to formulate the novel HMG-CoA reductase with arginine salt form in treatment of the disease condition since this salt selection process can be easily adopted in the drug development program for it's it well known effect as taught by Morris et al. As to claims 16 and 17 which claim a method of stimulating NO synthase administering Applicant's active agents said method involves a mechanism of action which is inherent in the treatment of medical disease condition.

Claims 1-6, 12, 13, 16-19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over McGovern et al.(U.S. Patent No. 5,634,895) and Igo et al.(U.S.Patent No. 5,634,895), all of record.

2. McGovern et al. on the abstract, teaches a method for preventing onset of restenosis after angioplasty employing a HMG-CoA reductase, pravastatin.

3. McGovern et al. on column 1, lines 26-40, reports that lovastatin, a HMG-CoA reductase inhibitor reduces restenosis following angioplasty.

4. Igo et al. teaches on the abstract, column 6, lines 41-44, column 7, lines 7-12, a method of treating angioplasty restenosis and **coronary blood vessels** by administering nitric oxide donor agent including L-arginine.

5. The claims differ from the cited references in claiming combination of L-arginine, and HMG-CoA reductase inhibitor, to treat a condition such as restenosis following

angioplasty. To employ combinations of L-arginine and HMG-CoA reductase inhibitor to treat a condition such as restenosis following angioplasty would have been obvious because all the components are well known individually for treating restenosis following angioplasty. It would be expected that the combination of components would treat restenosis following angioplasty as well.

The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). As to claims 16 and 17 which claim a method of stimulating NO synthase administering Applicant's active agents said method involves a mechanism of action which is inherent in the treatment of medical disease condition.

6. The therapeutic amounts of active agents to be used set forth in claims 6 and 17 and formulate prior to administration or mixed together in vivo set forth in claim 5, the route of administration set forth in claim 2, and setting a periodic indicator set forth in claim 19 are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional route of administration.

Claims 1,2,5,12, 13, 16, 17, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al.(1994), Pharmacol. Res. (1996)(U) and Bocan (U.S.Patent No.6,093,719) all of record.

7. Wang et al. teaches on the abstract, that the dietary L-arginine prevents **atherogenesis** in the coronary artery of the hypercholesterolemic rabbit.

8. The U reference teaches that cerivastatin interferes major process involved in **atherogenesis**.

9. Bocan on the abstract teaches atorvastatin alone resulting in a less **atherogenic** lipoprotein profile.

The claims differ from the cited references in claiming combination of L-arginine, and HMG-CoA reductase inhibitor, cerivastatin or atorvastatin to treat a condition such as atherogenesis. To employ combinations of L-arginine and cerivastatin or atorvastatin to treat a condition such as atherogenesis would have been obvious because all the components are well known individually for treating atherogenesis. It would be expected that the combination of components would treat atherogenesis as well. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). As to claims 16 and 17 which claim a method of stimulating NO synthase administering Applicant's active agents said method involves a mechanism of action which is inherent in the treatment of medical disease condition.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 703-308-2232. The examiner can normally be reached on Monday through Friday 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 703-305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Theodore J. Criares
Primary Examiner
Art Unit 1617

jmk
June 11, 2003